Inotropes, Vasopressors, and Chronotropes OH MY! A Review for the Young and the Seasoned

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I have nothing to disclose pertaining to this presentation
Objectives

- Review the mechanism of action for vasopressors and inotropes
- Recognize common side effects of different vasopressors and inotropes
- Review data for the use of alternative agents to treat vasoplegia
- Describe where angiotensin II fits into therapy
Clinical Scenarios

- Shock
  - Cardiogenic
  - Vasodilatory
- Sepsis
- Cardiac Surgery
- Valve Disease
- Decompensated Heart Failure

http://thefilmspectrum.com
The ultimate goal of cardiac function is **perfusion**

- Must deliver adequate oxygen to meet metabolic demand of end organs

Oxygen delivery is affected by multiple factors

- Hemoglobin
- Oxygen saturation
- Cardiac output

Cardiac Output (CO) = Heart Rate (HR) x Stroke Volume (SV)
Hemodynamics

\[ \text{CO} = \text{Heart Rate} \times \text{Stroke Volume} \]

- Heart Rate
  - Rate
  - Rhythm
- Stroke Volume
  - Preload
  - Contractility
  - Afterload
    - CVP
    - MAP
Vasopressors
Alpha Receptors

- **Alpha$_1$**
  - Located in vascular smooth muscle
  - Cause vasoconstriction
    - Skin, GI, Renal, Brain
- **Alpha$_2$**
  - Endocrine function
  - Negative feedback in neuronal synapse
Beta Receptors

- Beta$_1$
  - Located in cardiac tissue
  - Contractility and chronotropic effects
- Beta$_2$
  - Smooth muscle relaxation in bronchi and GI tract
- Beta$_3$
  - Lipolysis – may be a target for weight loss
Vasopressin Receptors

- $V_1$ receptor causes vasoconstriction in vascular smooth muscle
- $V_2$ receptor has an antidiuretic effect
- $V_3$ receptor is responsible for endocrine functions
<table>
<thead>
<tr>
<th>Medication</th>
<th>Alpha</th>
<th>Beta</th>
<th>Dopamine</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>+*</td>
<td>+*</td>
<td>+*</td>
<td>-</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Activity varies with dosing
Norepinephrine

- Has effect on both alpha and beta receptors
  - Primarily alpha causing vasoconstriction
  - Beta activity less than other vasopressors
- First line vasopressor in most clinical scenarios
  - SOAP-II trial
- Recommended as first-line agent in surviving sepsis guidelines
Epinephrine

- Has both vasopressor and inotrope activity
  - Could be considered an “ino-pressor”
- Both alpha and beta activity
  - Nearly equal on both
- Important to know what the titration goal is!
Phenylephrine

- Only has activity on alpha receptors
  - May be harmful in heart failure patients
- Misnomer that phenylephrine is safe to infuse via peripheral IV
  - Alpha receptors in peripheral tissue
  - Profound vasoconstriction leading to ischemia
Vasopressin

- Acts on vasopressin receptors to induce vasoconstriction
  - Differentiates from other vasopressors
  - Targeting alternate pathway may provide additional benefit
- Potential for gut ischemia due to vasoconstriction in splanchnic circulation
Dopamine

- Spectrum of primary activity is dose dependent
  - Affects dopamine, beta, and alpha receptors
- No longer considered a first line vasopressor in sepsis guidelines
  - Higher incidence of adverse effects than norepinephrine (SOAP II trial)
Dopamine Activity

<table>
<thead>
<tr>
<th></th>
<th>Alpha</th>
<th>Beta</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 mcg/kg/min</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>5-10 mcg/kg/min</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>&gt;10 mcg/kg/min</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

- Dopamine receptors induce urine production
- May be detrimental for monitoring
- *Not* renal protective
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochojad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*
SOAP II Trial

- All patients with shock were randomized for first-line vasopressor therapy
  - Dopamine: n = 858
  - Norepinephrine: n = 821
- Over 60% of patients with septic shock
- Primary outcome was 28 day mortality

# SOAP II Trial

## Table 2. Mortality Rates.*

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Dopamine</th>
<th>Norepinephrine</th>
<th>Odds Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During stay in intensive care unit</td>
<td>50.2</td>
<td>45.9</td>
<td>1.19 (0.98–1.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>During hospital stay</td>
<td>59.4</td>
<td>56.6</td>
<td>1.12 (0.92–1.37)</td>
<td>0.24</td>
</tr>
<tr>
<td>At 28 days</td>
<td>52.5</td>
<td>48.5</td>
<td>1.17 (0.97–1.42)</td>
<td>0.10</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>63.8</td>
<td>62.9</td>
<td>1.06 (0.86–1.31)</td>
<td>0.71</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>65.9</td>
<td>63.0</td>
<td>1.15 (0.91–1.46)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* Data were available for 1656 patients in the intensive care unit, in the hospital, and at 28 days; for 1443 patients at 6 months; and for 1036 patients at 12 months.

† Odds ratios for death are for the comparison of the dopamine group with the norepinephrine group.

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**Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.**

P = 0.07 by log-rank test

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## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td></td>
</tr>
<tr>
<td>New infectious episode</td>
<td></td>
</tr>
<tr>
<td>No. of episodes</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0–1</td>
</tr>
<tr>
<td>Patients with at least one episode — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Skin ischemia — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Mild†</td>
<td></td>
</tr>
<tr>
<td>Severe‡</td>
<td></td>
</tr>
<tr>
<td>Arterial occlusion — no. (%)‡‡</td>
<td></td>
</tr>
<tr>
<td>Arrows or fingers</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Impact

- Significantly more atrial fibrillation when dopamine used as primary vasopressor
- Dopamine and norepinephrine previously considered equivalent for sepsis patients
- Most recent surviving sepsis guidelines removed dopamine as primary vasopressor
Vasopressin versus Norepinephrine Infusion
in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D.,
Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D.,
John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D.,
and Dieter Ayers, M.Sc., for the VASST Investigators*
Randomized patients with septic shock already receiving norepinephrine

- Vasopressin 0.01 – 0.03 units/min
  - 397 patients assessed
- Norepinephrine 5 – 15 µg/min
  - 382 patients assessed

Primary endpoint was 28 day mortality
### Table 2. Analysis of the Rates and Risks of Death from Any Cause and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine Group (N=382)</th>
<th>Vasopressin Group (N=396)</th>
<th>P Value†</th>
<th>Absolute Risk Reduction (95% CI)‡</th>
<th>Relative Risk (95% CI)§</th>
<th>Adjusted Odds Ratio¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who underwent randomization and infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>150/382 (39.3)</td>
<td>140/396 (35.4)</td>
<td>0.26</td>
<td>3.9 (−2.9 to 10.7)</td>
<td>0.90 (0.75 to 1.08)</td>
<td>0.88 (0.62 to 1.26)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>188/379 (49.6)</td>
<td>172/392 (43.9)</td>
<td>0.11</td>
<td>5.7 (−1.3 to 12.8)</td>
<td>0.88 (0.76 to 1.03)</td>
<td>0.81 (0.57 to 1.16)</td>
</tr>
</tbody>
</table>

- †P value
- ‡Absolute risk reduction
- §Relative risk
- ¶Adjusted odds ratio

Clinical Impact

![Kaplan-Meier Survival Curves for Patients Who Underwent Randomization and Infusion.](image)

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

### Table 3. Serious Adverse Events in Patients Who Had Septic Shock.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine Group (N=382)</th>
<th>Vasopressin Group (N=396)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one serious adverse event</td>
<td>40 (10.5)</td>
<td>41 (10.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischemia</td>
<td>7 (1.8)</td>
<td>8 (2.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>8 (2.1)</td>
<td>3 (0.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
<td>6 (1.6)</td>
<td>3 (2.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Acute mesenteric ischemia</td>
<td>13 (3.4)</td>
<td>9 (2.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hyponatremia†</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Digital ischemia</td>
<td>2 (0.5)</td>
<td>8 (2.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other‡</td>
<td>2 (0.5)</td>
<td>5 (1.3)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

* Two-sided P values are based on Fisher's exact test.
† Hyponatremia was defined as a serum sodium level of less than 130 mmol per liter.
‡ Other events include acute hepatitis, agranulocytosis, pulmonary embolism, seizures, drug error, and two cases of drug extravasation from the central venous catheter.
Angiotensin II
Angiotensin II

- Newly approved by the FDA
- Indicated as an adjunct for patients with “high output shock”
- Angiotensin II for Treatment of Vasodilatory Shock (ATHOS-3) trial
  - Cardiac index >2.3 L/min/m²
  - Used in addition to other vasopressors (norepinephrine)
Hypotension

Baroreceptor Activation

Decreased Renal Perfusion

Increased Sympathetic Activity

RASS Activation

Cardiac Stimulation

Vasoconstriction

Volume Expansion

Increased HR and Contractility

Increased Systemic Vascular Resistance

Increased Preload

Increased Cardiac Output

Increased Cardiac Output

Increased Blood Pressure

Norepinephrine
Epinephrine
Dopamine
Phenylephrine

Vasopressin

Angiotensin II
## Pharmacokinetics/Pharmacodynamics

**Angiotensin II**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose</td>
<td>20 ng/kg/min</td>
</tr>
<tr>
<td>Titration</td>
<td>Up to 15 ng/kg/min every 5 min</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>80 ng/kg/min (initial)</td>
</tr>
<tr>
<td></td>
<td>40 ng/kg/min (maintenance)</td>
</tr>
<tr>
<td>Time to Effect</td>
<td>5 minutes to reach target MAP</td>
</tr>
<tr>
<td>Plasma Half-Life</td>
<td>&lt;1 minute</td>
</tr>
<tr>
<td>Pertinent Adverse Effects</td>
<td>Thromboembolic events (12.9%)</td>
</tr>
<tr>
<td>Medication Interactions</td>
<td>ACE inhibitors, ARBs</td>
</tr>
</tbody>
</table>

Giapreza [Package Insert]. San Diego, CA: La Jolla Pharmaceutical; 2017
Clinical Implications

- Utilization of alternative mechanism to increase vasoconstriction
- Potential for use in cardiogenic shock?
  - Inotropes
  - Mechanical support
- Ongoing Phase IV monitoring for adverse events
- Availability in the short term is complicated
Inotropes
## Receptor Targets

<table>
<thead>
<tr>
<th>Medication</th>
<th>Alpha</th>
<th>Beta</th>
<th>Dopamine</th>
<th>PDE-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>+*</td>
<td>+*</td>
<td>+*</td>
<td>-</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Milrinone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

*Activity varies with dosing*
Dobutamine

- Exclusively has beta activity
  - Increases heart rate and contractility
  - Both affecting cardiac output
- Half-life of only a few minutes
- Tachycardia and arrhythmia are the most prominent adverse effects
Milrinone

- Phosphodiesterase inhibition (PDE-3) leads to increased c-AMP and more contractility
  - Alternative mechanism from other inotropes
  - Often used in combination
- Half-life of a few hours
  - Arrhythmia potential is major concern
  - Not as easily titratable
- Vasodilation through PDE inhibition
Epinephrine

- Mixed alpha and beta activity
- Dual effects can be a pro or con
  - Advantage to using a single drug
  - Titration can be difficult
- Proarrhythmic effects can help guide titration with other inotropes
Agent Selection

- Utilize alternative receptor profiles for synergistic effect
  - Addition of drug with same receptor profile will limit the return on investment
  - Understanding the mechanism of each drug is essential for selection
- Recognize potential adverse effects of each medication
Alternative Agents
Vasoplegia

- Vasodilatory shock resulting from cardiopulmonary bypass (CPB)
  - Occurs in 8 – 10% of cardiac surgery patients
    - Higher incidence for specific surgeries
  - High doses of vasopressors are often needed to maintain an adequate MAP
- Vasoplegia may result from a dysregulation of nitric oxide (NO) synthesis

Vasoplegia Mechanism

Angiotensin II

Nitric Oxide

Atrial Natriuretic Peptide

Norepinephrine

Calcium Stores

Myosin

Ca^{2+}

Vasoconstriction

cGMP

Myosin Phosphatase

Myosin Phosphatase

Vasodilation

Cytoplasm

Plasma Membrane

J Cardiothorac Vasc Anesth. 2017 Oct 27
Vasoplegia Mechanism

- ↑ Nitric Oxide Synthase
- ↑ Nitric Oxide
- ↑ cGMP
- ↓ Cytoplasmic Ca²⁺
- ↓ Phosphorylated Myosin
- → Open K_{ATP}
- ↓ ATP, ↑ H⁺, ↑ Lactate in Vascular Smooth Muscle
- ↑ Vasopressin Secretion
- ↓ Vasopressin Stores
- ↓ Plasma Vasopressin

J Cardiothorac Vasc Anesth. 2017 Oct 27
Methylene Blue

- Used as a diagnostic agent (dye)
- Methemoglobinemia treatment
  - Cofactor for NADPH reducing methemoglobin to hemoglobin (doses >4 mg/kg)
- Inhibition of guanylate cyclase may be beneficial for vasoplegia/shock
Methylene Blue

- Used off label for vasoplegia during cardiac surgery
- Direct inhibition of nitric oxide synthesis
  - Also blocks cyclic guanosine monophosphate (cGMP)
- Dosing: 1.5 – 2 mg/kg over 20-60 minutes
  - Continuous infusion: 0.5 – 1 mg/kg/hr after bolus dose
- Prospective data is lacking to show effects
  - Timing of use may limit data on effectiveness

Methylene Blue – Adverse Effects

- Contraindicated with G6PD deficiency
- Blue discoloration of skin and body fluids
- Interaction with pulse oximetry
  - Oxygen saturation may be falsely low
- Increase in pulmonary artery pressure
- Inhibition of monoamine oxidase
  - Can precipitate serotonin syndrome

Pharmacotherapy. 2010 Jul;30(7):702-15
J Cardiothorac Vasc Anesth. 2017 Oct 27
Hydroxocobalamin

- Used for the treatment of cyanide toxicity
- Case reports for use of hydroxocobalamin to treat vasoplegia
  - Including at least 1 report of treating methylene blue resistant vasoplegia
- Dosing extrapolated from cyanide toxicity treatment

Hydroxocobalamin

- Case reports for use of high dose vitamin B12 to reverse vasoplegia after cardiac surgery
- Proposed mechanism is NO scavenging
- Dose: 5 grams IV once
  - Rapid weaning from vasopressor support may be possible

Hydroxocobalamin – Adverse Effects

- Does not have the risk of serotonin syndrome that methylene blue has
  - Important consideration when deciding on agent to use
- Discoloration of urine – different from methylene blue
- My be cost-prohibitive and/or logistically difficult to acquire
Summary

- Understanding individual patient physiology can guide drug choice
- Norepinephrine is first line vasopressor in majority of patients (SOAP II data)
- Titration of vasopressin may or may not be allowed at your institution
Summary

- Understanding receptor activity is essential for optimizing vasopressor/inotrope therapy
- Angiotensin II provides novel mechanism for vasoconstriction
  - Role in therapy not yet solidified
- Methylene blue or hydroxocobalamin may be used as salvage therapy, especially for CPB associated vasoplegia
Questions?